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(71) Applicant *(for all designated States except US)*: G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680–5110 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ALEXANDER, John, C. [US/US]; 1100 Pelham Road, Winnetka, IL 60093 (US). RONIKER, Barbara [US/US]; 1530 North Dearborn Parkway, Chicago, IL 60610 (US). DESAI, Subhash [US/US]; 1011 Greenwood Avenue, Wilmette, IL 60091 (US).

(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680–5110 (US).

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(54) Title: COMBINATION THERAPY OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR AND EPOXY–STEROIDAL ALDOSTERONE ANTAGONIST FOR TREATMENT OF CARDIOVASCULAR DISEASE

(57) Abstract

Combinations of an ACE inhibitor and an epoxy–steroidal aldosterone receptor antagonist are described for use in treatment of circulatory disorders. Of particular interest are therapies using epoxy–steroidal–type aldosterone receptor antagonist compounds, such as eplerenone, in combination with an angiotensin converting enzyme inhibitor. This co–therapy would be particularly useful to treat congestive heart failure while avoiding or reducing aldosterone–antagonist–induced side effects such as hyperkalemia.

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COMBINATION THERAPY OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR AND EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST FOR TREATMENT OF CARDIOVASCULAR DISEASE

Cross-Reference to Related Applications

This application claims priority of U.S. provisional application Ser. No. 60/122,997 filed March 05, 1999 and U.S. provisional application Ser. No. 60/122,998 filed March 05, 1999.

Field of the Invention

Combinations of an angiotensin converting enzyme inhibitor and an epoxy-steroidal aldosterone receptor antagonist are described for use in treatment of circulatory disorders, including cardiovascular diseases such as heart failure, hypertension and congestive heart failure. Of particular interest are therapies using epoxy-steroidal-type aldosterone receptor antagonist compound eplerenone in combination with an angiotensin converting enzyme inhibitor.

Background of the Invention

Myocardial (or cardiac) failure, whether a consequence of previous myocardial infarction(s), heart disease associated with hypertension, or primary cardiomyopathy, is a major health problem of worldwide proportions. The incidence of symptomatic heart failure has risen steadily over the past several decades.

In clinical terms, decompensated cardiac failure consists of a constellation of signs and symptoms that arise from congested organs and hypoperfused tissues to

form the congestive heart failure (CHF) syndrome. Congestion is caused largely by increased venous pressure and by inadequate sodium (Na^+) excretion, relative to dietary Na^+ intake, and is importantly related to circulating levels of aldosterone (ALDO). An abnormal retention of Na^+ occurs via tubular epithelial cells throughout the nephron, including the later portion of the distal tubule and cortical collecting ducts, where ALDO receptor sites are present.

ALDO is the body's most potent mineralocorticoid hormone. As connoted by the term mineralocorticoid, this steroid hormone has mineral-regulating activity. It promotes Na+ reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive tissues. ALDO regulates Na+ and water resorption at the expense of potassium (K^+) and magnesium (Mg^{2+}) excretion.

Aldosterone plays an important role in the pathophysiology of heart failure (HF) (Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. Circulation 1981; 63 (3):645-651). Aldosterone promotes sodium retention, magnesium and potassium loss (which contributes to arrhythmias and sudden cardiac death), sympathetic activation and parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, impaired arterial compliance, and vascular damage. (Wang W. Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. Hypertension 1994;24(5):571-575;). Chronic elevations in circulating aldosterone levels result in fibrous tissue formation in the heart and vessels, which contributes to progressive HF. (Weber

KT, et al. Collagen in the hypertrophied pressure-overloaded myocardium. Cir 1987;75:140-147). An increase in myocardial collagen production and subsequent left ventricular (LV) hypertrophy leads to myocardial stiffness, reduced ventricular and vascular compliance, impaired diastolic filling, diastolic and systolic dysfunction, ischemia, and ultimately HF. Myocardial fibrosis can also lead to arrhythmias and sudden death. Aldosterone blocks myocardial norepinephrine uptake, increases plasma norepinephrine, and promotes ventricular ectopic activity. (Struthers AD. Aldosterone escape during ACE inhibitor therapy in chronic heart failure. Eur Heart J 1995;16(Suppl N):103-106; Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. J Cardiac Failure 1996; 2(1):47-54). Aldosterone affects baroreceptor function and causes cerebro- and renal vascular damage as well as endothelial dysfunction. (Struthers AD. Aldosterone escape during ACE inhibitor therapy in chronic heart failure. Eur Heart J 1995;16(Suppl N):103-106). Aldosterone also has been shown to increase plasminogen activator inhibitor levels and thereby may impede fibrinolysis.

ALDO can also provoke responses in nonepithelial cells. Elicited by a chronic elevation in plasma ALDO level that is inappropriate relative to dietary Na^+ intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as non-renin-dependent factors (such as K^+, ACTH) that

promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine its plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

The renin-angiotensin-aldosterone system ("RAAS") is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension, a precursor conditon implicated in the progression of more serious cardiovascular diseases such as congestive heart failure. Activation of the renin-angiotensin-aldosterone system begins with secretion of the enzyme renin from the juxtaglomerular cells in the kidney. The enzyme renin acts on a naturally-occurring substrate, angiotensinogen, to release a decapeptide, Angiotensin I. This decapeptide is cleaved by angiotensin converting enzyme ("ACE") to provide an octapeptide, Angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic effect and modulating other hormonal systems.

Emphasis has been placed on minimizing hyperaldosteronism as a basis for optimizing patient treatment. Many clinicians have assumed that the inhibition of the renin angiotensin aldosterone system (RAAS) by an angiotensin-converting enzyme inhibitor (ACE-I) will prevent aldosterone formation. However, increasing evidence suggests that ACE-I only transiently suppresses aldosterone levels. (Struthers AD.

Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. J Cardiac Failure 1996; 2(1):47-54). Plasma aldosterone levels decrease initially with ACE-I treatment, but return to pretreatment levels after three to six months of ACE-I therapy, despite good compliance with continued drug administration. (Staessen J, Lijnen P, Fagard R, Verschueren LJ, Amery A. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. J Endocr 1981;91:457-465) This phenomenon is known as aldosterone "escape," since there are other important determinants of aldosterone release, such as serum potassium. (Pitt B. "Escape" of aldosterone production in patients with left ventricular dysfunction treated with an angiotensin converting enzyme inhibitor: implications for therapy. Cardiovascular Drugs and Therapy 1995;9:145-149).

Attempts to reduce ALDO-receptor antagonism both in patients treated with conventional diuretic programs and in patients treated with angiotensin-converting enzyme (ACE) inhibitors, who are often constrained to small doses of ACE inhibitor because of orthostatic hypotension. Such patients may demonstrate a recurrence of heart failure symptoms likely related to elevations in plasma ALDO levels.

Blockade of aldosterone with ACE-I has been shown to have a beneficial effect on survival and hospitalization in patients with HF. In the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial, mortality at one year was reduced by 31% in patients with severe HF (NYHA Class IV) treated with enalapril (an ACE-I) plus diuretics compared to placebo plus diuretics. In CONSENSUS, patients with high baseline plasma aldosterone levels had a higher mortality than patients with low

baseline levels. In the group treated with enalapril, mortality was reduced only in the group with baseline aldosterone plasma levels above the median. In the group whose baseline aldosterone plasma levels were below the median, no difference from placebo in mortality was observed. (Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990; 82(5):1730-1736).

Aldosterone receptor antagonists act directly by blocking aldosterone's site of action. Aldosterone receptor blocking agents have not been widely used in conjunction with ACE-I because of the potential for serious hyperkalemia. However, in the Randomized ALdactone Evaluation Study (RALES), the addition of spironolactone 25 mg daily, a dose which is neither diuretic nor hemodynamic, to standard therapy (ACE-I and loop diuretic, with or without digoxin) in the treatment of patients with severe HF (NYHA Class III or IV) resulted in a 30 percent risk reduction for all cause mortality compared to patients treated with standard therapy plus placebo ($p<0.001$). Patients treated with spironolactone also had a 35 percent lower frequency of hospitalization for worsening HF than placebo patients. (Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341(10):709-717) It should be emphasized that these improvements in mortality and morbidity occurred when spironolactone was added to standard therapy, which included ACE-I. Patients treated with spironolactone had a median increase in serum potassium concentration that

was statistically but not clinically significant compared to patients treated with placebo.

Patients who experience acute myocardial infarction (AMI) often go on to develop HF and subsequent death. Blockade of the RAAS by ACE-I has been shown to reduce all cause mortality in such patients. In the Acute Infarction Ramipril Efficacy Study (AIRE), administration of an ACE-I to patients with clinical evidence of HF at any time after an AMI resulted in a risk reduction of 27% in all cause mortality compared to placebo (p=0.002). (The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821-828) Moreover, there was a 23% reduction in the risk of developing severe resistant HF in treated patients compared to placebo (p=0.017). (Cleland JGF, Erhardt L, Murray F, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure: a report from the AIRE Study Investigtors. Eur Heart J 1997;18:41-51) In a long-term (three year) follow-up of the AIRE patients (AIREX), Hall et al. found that patients treated with ACE-I had a risk reduction in all cause mortality of 36% compared to placebo (p=0.002), suggesting that inhibition of the RAAS after AMI has not only a significant impact on survival, but also a long term one. (Hall AS, Murray GD, Ball SG on behalf of the AIREX Study Investigators. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Lancet 1997;349(9064):1493-1497) In another post-MI study (Trandolapril Cardiac Evaluation study, TRACE), patients with LV dysfunction 2 to 6 days following MI treated with ACE-I had a relative

reduction in the risk of death of 18% compared to placebo (p=0.001), and a reduction of 29% compared to placebo in the risk of progression to severe HF (p=0.003). (Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbæk J, Cole DS, Auclert L, Pauly NC, Aliot E, Persson S, Camm AJ for the Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670-1676; Torp-Pedersen C, Køber L, Carlsen J on behalf of the TRACE Study Group. Angiotensin-converting enzyme inhibition after myocardial infarction: the trandolapril cardiac evaluation study. Am Heart J 1996;132:235-243) In a study of ramipril versus spironolactone, Rodriguez et al (found that both drugs prevented ventricular dilatation and further decline of systolic dysfunction in patients with impaired ejection fraction post AMI. The results of these studies suggest that the addition of an aldosterone receptor antagonist to an ACE-I in patients following an AMI will further reduce mortality. (Rodriguez JA, Godoy I, Castro P, Quintana JC, Chavez E, Corbalan R. A double-blind randomized placebo controlled study of ramipril vs. spironolactone on left ventricular remodeling after acute myocardial infarction. JACC 1997;abstract 947-9:133A)

Many aldosterone receptor blocking drugs and their effects in humans are known. For example, spironolactone is a drug which acts at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosterone-related diseases such as liver cirrhosis

and congestive heart failure [F.J. Saunders et al, Aldactone; Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day] was administered to a spironolactone-intolerant patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug, 1986)]. It has been recognized that development of myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to excessive collagen deposition [D. Klug et al, Am. J. Cardiol., 71 (3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G. Brilla et al, J. Mol. Cell. Cardiol., 25 (5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)].

Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of Angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

Moreover, although ACE inhibitors effectively block the formation of Angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, J. Endocrinol., 91, 457-465 (1981)]. A similar effect has been observed for patients with myocardial infarction receiving zofenopril [C. Borghi et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. Patients suffering from cardiovascular diseases are also often put on low sodium diets. This regimen can induce an increase in aldosterone production and an increase in angiotensin receptors which stimulate aldosterone synthesis. Thus, a patient on a low sodium diet may induce a condition of hyperaldosteronism even in the presence of an ACE inhibitor. This phenomenon has been termed "aldosterone escape". In a side-by-side treatment of two cohorts of rats, one cohort treated with spironolactone sub-cutaneously and the other cohort treated with captopril, spironolactone was found to prevent fibrosis in the hypertensive-rat cohort [C.G. Brilla et al, J. Mol. Cell. Cardiol., 25, 563-575 (1993)].

Another series of steroidal-type aldosterone receptor antagonists is exemplified by epoxy-containing spironolactone derivatives. For example, U.S. Patent No. 4,559,332 issued to Grob et al describes 9a,11a-epoxy-containing spironolactone derivatives as aldosterone antagonists useful as diuretics. These 9a,11a-epoxy steroids have been evaluated for endocrine effects in comparison to spironolactone [M. de Gasparo et al, J. Pharm. Exp. Ther., 240(2), 650-656 (1987)].

Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and that aldosterone levels increase as CHF progresses from RAAS activation. Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. Cardiol., 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of captopril and spironolactone was administered and found effective to control refractory CHF without serious incidents of hyperkalemia. [U. Dahlstrom et al, Am. J. Cardiol., 71, 29A-33A (21 Jan 1993)]. Spironolactone coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure [A.A. van Vliet et al, Am. J. Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)]. PCT Application Ser. No. US 96/01969 published 15 August 1996 describes a combination therapy of an ACE Inhibitor and a side-effect reduced amount of an aldosterone antagonist, namely, spironolactone, to treat congestive heart failure. PCT Application Ser. No. US96/01764 published

15 August 1996 describes a combination therapy of an ACE Inhibitor and a side-effect reduced amount of an aldosterone antagonist, namely, spironolactone, and a diuretic, such as a loop diuretic, to treat congestive heart failure.

Combinations of an angiotensin II receptor antagonist and aldosterone receptor antagonist are known. For example, PCT Application No. US91/09362 published 25 June 1992 describes treatment of hypertension using a combination of an imidazole-containing angiotensin II antagonist compound and a diuretic such as spironolactone. PCT Application Ser. No. US96/09342 published 19 December 1996 describes treatment of congestive heart failure with a combination of an angiotensin II antagonist and the aldosterone receptor antagonist spironolactone. PCT Application Ser. No. US96/08823 published 19 December 1996 describes treatment of myocardial fibrosis with a combination of an angiotensin II antagonist and the aldosterone receptor antagonist spironolactone. PCT Application Ser. No. US96/09335 published 19 December 1996 describes treatment of congestive heart failure with a combination of an angiotension II antagonist and the epoxy-steroidal aldosterone antagonist epoxymexrenone. PCT Application Ser. No. US96/08709 published 19 December 1996 describes treatment of cardiofibrosis with a combination of an angiotensin II antagonist and the epoxy-steroidal aldosterone receptor antagonist epoxymexrenone.

What Is Claimed Is:

1. A combination comprising a therapeutically-effective amount of an angiotensin converting enzyme inhibitor and an epoxy-steroidal aldosterone receptor antagonist, said epoxy-steroidal aldosterone receptor antagonist being present in an amount which is therapeutically effective to antagonize aldosterone but which amount is not sufficient for said aldosterone receptor antagonist to induce a substantially adverse side effect.

2. The combination of Claim 1 wherein said aldosterone receptor antagonist is an epoxy-steroidal-type compound characterized in having a 9α-,11α-substituted epoxy moiety.

3. The combination of Claim 2 wherein said epoxy-steroidal-type compound is eplerenone.

4. The combination of Claim 1 wherein angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat, spirapril, Bioproject BP1.137, Chiesi CHF 1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat, and Servier S-5590.

5. The combination of Claim 4 wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril,

trandolapril, ceranapril, moexipril, quinaprilat, and spirapril.

6. The combination of Claim 1 further characterized by said angiotensin converting enzyme inhibitor and said aldosterone receptor antagonist being present in said combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of said angiotensin converting enzyme inhibitor to said aldosterone receptor antagonist.

7. The combination of Claim 6 wherein said weight ratio range is from about one-to-one to about fifteen-to-one.

8. The combination of Claim 7 wherein said weight ratio range is from about one-to-one to about five-to-one.

9. A combination therapy for treating cardiovascular disorders in a subject afflicted with or susceptible to multiple cardiovascular disorders, wherein said combination therapy comprises administering a therapeutically-effective amount of a two-component combination consisting essentially of an angiotensin converting enzyme inhibitor as a first component and an epoxy-steroidal aldosterone receptor antagonist as a second component in an amount therapeutically effective to antagonize aldosterone but insufficient to induce an adverse side effect.

10. The combination therapy of Claim 9 wherein said subject is afflicted with or susceptible to heart failure and said subject further requires avoidance of the incidence of hyperkalemia.

11. The combination therapy of Claim 10 wherein said subject is further susceptible to congestive heart failure.

12. The combination therapy of Claim 10 wherein said subject is further susceptible to hypertension.

13. The combination therapy of Claim 10 further characterized by administering said angiotensin converting enzyme inhibitor and said epoxy-steroidal aldosterone receptor antagonist.

14. The combination therapy of Claim 10 further characterized by administering said angiotensin converting enzyme inhibitor and said epoxy-steroidal aldosterone receptor antagonist in a substantially simultaneous manner.

15. The combination therapy of Claim 9 wherein said epoxy-steroidal aldosterone receptor antagonist is a compound characterized in having a 9α-11α-substituted epoxy moiety.

16. The combination therapy of Claim 15 wherein said epoxy-steroidal compound is eplerenone.

17. The combination therapy of Claim 9 wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat, spirapril, Bioproject BP1.137, Chiesi CHF 1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat, and Servier S-5590.

18. The combination therapy of Claim 17 wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat, and spirapril.

19. The combination therapy of Claim 9 further characterized by said angiotensin converting enzyme inhibitor and said epoxy-steroidal aldosterone receptor antagonist being used in said co-therapy in a weight ratio range from about 0.5-to-one to about twenty-to-one of said angiotensin converting enzyme inhibitor to said aldosterone receptor antagonist.

20. The combination therapy of Claim 19 wherein said weight ratio range is from about one-to-one to about fifteen-to-one.

21. The combination therapy of Claim 20 wherein said weight ratio range is from about one-to-one to about five-to-one.

22. The combination therapy of Claim 9 wherein said angiotensin converting enzyme inhibitor is captopril, in a dose range from about 40 mg to about 80 mg per dose, or is enalapril in a dose range from about 5 mg to about 25 mg per dose.

23. The combination therapy of Claim 22 wherein said epoxy-steroidal aldosterone receptor antagonist is eplerenone in a dose range from about 25 mg to about 100 mg per dose.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 00/05633

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K38/55 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40257 A (G.D. SEARLE) 19 December 1996 (1996-12-19) cited in the application claims 1-5,17-21,23,28-32,44,45 page 9, line 26-37 page 11 page 191, line 18-23	1-23
X	WO 96 40255 A (G.D. SEARLE) 19 December 1996 (1996-12-19) cited in the application claims 1-5,17-20 page 1, line 17-22 page 9, line 24-35 page 11 page 191, line 18-23	1-23

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[X] Further documents are listed in the continuation of box C.

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

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Inte onal Application No
PCT/US 00/05633

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